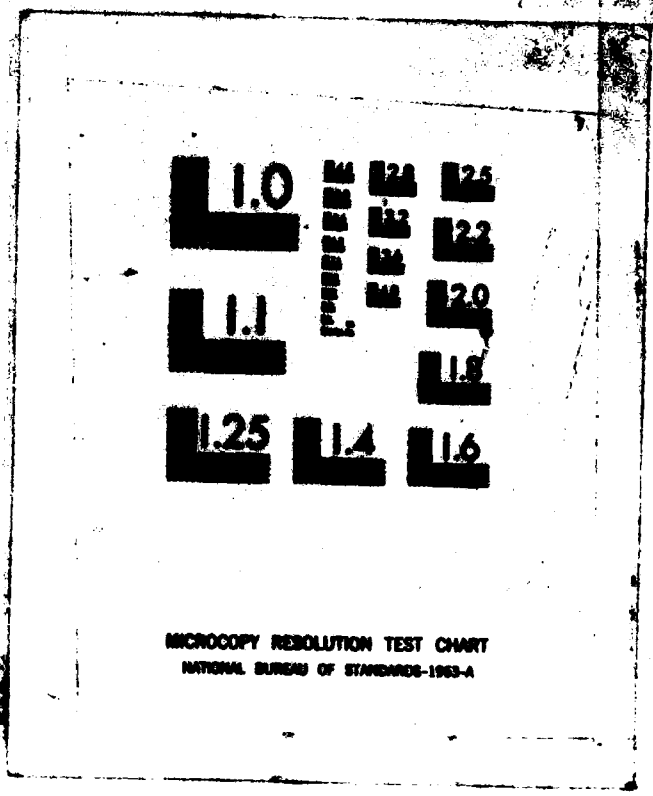
AD-A181 670 CLINICAL PHARMACOLOGY STUDIES PHASE 1(U) JOHNS HOPKINS 1/1
UNIV BALTIMORE MD DIV OF CLINICAL PHARMACOLOGY
P S LIETMAN ET AL. 15 APR 87 DAMD17-85-C-5133

UNCLASSIFIED F/G 6/15 NL


1.0
1.1
1.25
1.4
1.6
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

Phase I Clinical Pharmacology Studies (U)
ANNUAL REPORT

Paul S. Lietman, M.D., Ph.D.
Brent G. Petty, M.D.
David M. Kornhauser, M.D.

April 15, 1987

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Maryland 21701-5012

Contract No. DAMD17-85-C-5133

Division of Clinical Pharmacology
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205

AD-A181 670

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution is unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Div. of Clinical Pharmacology, The Johns Hopkins University School of Medicine; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): 600 N. Wolfe Street, Baltimore, Maryland 21205	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: USAMRDC; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-85-C-5133
8c. ADDRESS (City, State, and ZIP Code): Ft. Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
63751 A	3M463. 751D993	AE	165

11. TITLE (Include Security Classification)
Phase I Clinical Pharmacology Studies

12. PERSONAL AUTHOR(S)
Paul S. Lietman, M.D., Ph.D., Brent G. Petty, M.D., David M. Kornhauser, M.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 6/1/85 TO 12/31/86	1987, April 15	16

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	01		Pyridostigmine, WR 6026, leishmaniasis, organophosphate poisoning, pharmacokinetics, pharmacodynamics, acetyl-cholinesterase
06	15		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Description of overall scope of contract.

Description of activities regarding organization of efforts under the contract (Task Order #1).

Description of pyridostigmine pharmacokinetics and pharmacodynamic evaluation (Task Order #2).

Description of WR 6026 safety, tolerance, and pharmacokinetic study (Task Order #3).

Description of protocol preparation for continuous intravenous infusion of pyridostigmine with evaluation of effects before, at, and after steady state (Task Order #4).

Description of protocol preparation for oral sustained-release pyridostigmine absorption, pharmacokinetic, and pharmacodynamic study (Task Order #5).

Description of evolution of a new method for interacting with the sponsor, ultimately leading to Task Order #6.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
	(301) 663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

AD_____

Phase I Clinical Pharmacology Studies (U)
ANNUAL REPORT

Paul S. Lietman, M.D., Ph.D.
Brent G. Petty, M.D.
David M. Kornhauser, M.D.

April 15, 1987

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Maryland 21701-5012

Contract No. DAMD17-85-C-5133

Division of Clinical Pharmacology
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205

Summary

The "first year" of this contract began June 1, 1985 and was extended to December 31, 1986. This contract was established to allow the Division of Clinical Pharmacology at The Johns Hopkins University School of Medicine to assist the U.S. Army Medical Research and Development Command (USAMRDC) in its drug development efforts. In particular, the contract originally was designed to provide the resources and expertise needed to conduct excellent Phase I clinical trials of compounds under development by the Army drug development program. It was our original hope, however, that the interaction between the parties would transcend a simple sponsor-contractor relationship and instead flourish into a collegial relationship wherein a wide variety of current and future compounds and questions would be addressed. We believe that this collegial relationship has, in fact, developed between the Division of Experimental Therapeutics (WRAIR) and the Division of Clinical Pharmacology (J.H.U.) to the mutual benefit of both parties.

The scientific work of this year centered around ~~(1)~~ the bioavailability, safety, tolerance, pharmacokinetics and pharmacodynamics of pyridostigmine; and ~~(2)~~ the absorption, safety, tolerance and pharmacokinetics of single doses of WR 6026. These two studies were completed successfully and efficiently, and complete details can be found in the draft Task Reports which have been submitted. These drafts are in the process of review and revision by Division of Experimental Therapeutics personnel prior to publication of final Task Reports.

Two draft protocols for future studies were also completed in the "first year" in response to Task Orders #4 and #5. These protocols were submitted for review by WRAIR personnel, and we anticipate that they will be initiated early in the second year of the contract.

We believe that with the work accomplished in the "first year" and the development of Task Order #6 to facilitate the development of future protocols and other collaborative efforts, the Army's drug development Phase I program is now poised to make substantial progress in the next two years.

Foreword

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects the investigators have adhered to policies of applicable Fedral Law 45CFR46.

Table of Contents

1. STATEMENT OF THE PROBLEM

The objective of the contract is "to carry out Phase I Clinical Pharmacology Studies (safety, tolerance, and/or pharmacokinetics) in humans." These studies support the U. S. Army Drug Development Program.

2. BACKGROUND

This contract is the result of a solicitation (DAMD 17-84-R-0074) issued by the U. S. Army Medical Research Acquisition Agency on September 24, 1984 entitled "Phase I Clinical Pharmacology Studies" and the response to that solicitation by The Johns Hopkins University School of Medicine on October 31, 1984 consisting of a Technical Proposal and a Business Proposal entitled "Phase I Clinical Pharmacology Studies." The contract was signed on behalf of The Johns Hopkins University on May 23, 1985 and on behalf of The U. S. Army Medical Research and Development Command on May 24, 1985. The effective date of the contract was June 1, 1985 and the original term of the contract was to May 31, 1986. The term of the contract was extended to September 1, 1986 on May 21, 1986 and to December 31, 1986 on September 29, 1986. Thus, this "annual" report will cover the nineteen-month period from June 1, 1985 through December 31, 1986.

3. APPROACH TO THE PROBLEM

The approach to the problem that we have taken involves the provision of carefully conducted Phase I clinical pharmacology studies as specified by the individual Task Orders provided by the Army and, in addition, the development of a working relationship between the involved faculty of The Johns Hopkins University School of Medicine and the involved personnel of The U. S. Army Drug Development Program. This relationship fosters the development of studies that are optimal with respect to quality and efficiency.

4. RESULTS

The results that have been realized from the first nineteen-month term of this contract will be presented in two parts. The first section will deal with general aspects of the contract and the second section will deal with the specific Task Orders that have constituted the scientific work requested by the Army.

5. RESULTS - GENERAL

This section will be presented in a format that follows, in general, the outline of the contract.

5.1 Scope of Work

The contract was originally written in a manner that described in broad and non-specific terms the scope of work anticipated by the Army. In actuality the scope of work during this initial nineteen-month period has been less than anticipated based on the original RFP and contract. Each proposed study has been accepted and two have been completed. The specifics of the studies are summarized below under specific task orders.

5.2 Study Population

A population of male volunteers of legal age (but age 35 years or less) has been identified and organized in a manner that promotes the efficient selection of appropriate subjects for each study. This pool of available volunteers is continuously updated and expanded. Recruitment and screening of potential volunteers occurred throughout the period of the contract.

The "Requirements for the Use of Humans," as defined in Section H.1.b. of the contract, have been strictly followed including Institutional Review Board (The Johns Hopkins Medical Institutions' Joint Committee on Clinical Investigation) approval of each study involving human subjects; provision of an appropriate HHS Form 596 for each study; and adherence to the requirements of "Title 45, Part 46 of the CFR" as specified in Section H.1.b.(3) of the contract.

5.3 Facilities

A clinical test facility has been provided that offers the requisite equipment and supplies as specified in Section C.3.a. of the contract.

A laboratory facility has been provided in adherence to the specifications of Section C.3.b. of the contract.

In addition, a research laboratory facility has been provided in order to provide immediate and accurate acetylcholinesterase levels as required by the Army in Task Order #2. The development of this capability was in close collaboration with A. Kaminskis of the Analytical Chemistry Branch of the U. S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland.

6. RESULTS - SPECIFIC

This section will be presented in a format based on specific Task Orders.

6.1 Task Order #1

This task order was for the following:

6.1.1 Organize the overall work of the contract.

6.1.2 Order supplies and equipment.

6.1.3 Recruit and screen subjects.

6.1.4 Indirect costs for the above would be charged to this task order.

This task order provided for the necessary start-up costs and ongoing costs to support the Army's mission throughout the nineteen months of the period.

The task order was issued on June 3, 1985, delivered to us on June 7, 1985 and accepted by us on June 17, 1985. A budget revision was submitted by us on August 1, 1985. A specific request to purchase approved equipment was submitted by us on January 14, 1986 and approval was granted on March 7, 1986. A specific request for permission to use travel money for foreign travel was submitted on May 23, 1986 and denied.

A revision of the budget for Task Order #1 was submitted by us on May 23, 1986. More specific justification was sought on October 8, 1986. The final revision of the budget for Task Order #1 was approved on November 24, 1986.

In general, this task order has been carried out:

(1) The overall work of the contract has been organized. In addition to the organization of the specific task orders we have collaborated with the U. S. Army Drug Development Program in organizing a plan that will enhance the efficiency of interacting with the Army to the advantage of the Army. This plan has been formalized as Task Order #6 which has been implemented at the start of the second year of the contract.

(2) The requisite supplies and equipment were purchased.

(3) An effective and on-going method of recruiting and screening subjects was organized and implemented.

7.1 Task Order #2

This task order, issued on June 5, 1985 was for the following objective.

7.1.1 "Determine the comparative bioavailability of oral Mestinon (Roche) syrup (60 mg/5 ml) to intravenous Mestinon (10 mg/2 ml). Data obtained from this study will be utilized in follow-on development of an oral, sustained-release formulation. Data will also be utilized to determine the correlation between pyridostigmine serum levels and acetylcholinesterase inhibition." The "deliverables" included:

7.1.1.1 Task schedule (projected time frame for conducting study).

7.1.1.2 Draft protocol.

7.1.1.3 Final protocol (to include any modifications).

7.1.1.4 Task report (Study report).

7.1.1.5 Budget data, as per contract.

Task Order #2 was completed and can be summarized as follows:

The first six subjects received oral and intravenous pyridostigmine (in a dose-ranging phase) in an effort to approach, but not exceed, 40% inhibition of erythrocyte acetylcholinesterase. After the proper dose was determined, 18 additional subjects received oral and intravenous pyridostigmine to address the objectives mentioned above.

The subjects were monitored for toxicity with clinical laboratory tests of hematology and chemistry parameters, electrocardiograms, vital signs, and coordination testing. All of the subjects tolerated pyridostigmine well, with no adverse symptoms. One subject developed a significant increase in serum creatine kinase and 2 subjects had trivial elevations in liver enzymes. No significant changes occurred in electrocardiograms, vital signs, coordination, or other clinical laboratory tests.

The mean bioavailability of oral pyridostsigmine syrup was 29.2%, although there was considerable interindividual variability with a range of 14.7% to 51.1%.

The pharmacokinetics of both oral and intravenous pyridostigmine were defined and considerable interindividual variability was also observed in the rate of elimination. The mean total clearance was 779 mL/min with a range of 381 mL/min to 1,511 mL/min, and the mean beta half-life was 0.8 hours with a range of 0.36 to 3.2 hours.

The relationship between pyridostigmine plasma levels and erythrocyte acetylcholinesterase inhibition was defined after both oral and intravenous pyridostigmine administration. The erythrocyte acetylcholinesterase inhibition was delayed in both onset and dissipation compared to plasma pyridostigmine levels. Furthermore, there was an additional two-fold variability between subjects with respect to the extent of enzyme inhibition at a given plasma level.

8.1. Task Order #3

This task order, issued on March 13, 1986, was "To determine the pharmacokinetics of WR 6026 hydrochloride in healthy volunteers given a single oral dose at 60 mg."

Task Order #3 was completed and can be summarized as follows:

Eight subjects who gave written informed consent participated in this study which was conducted in the Clinical Pharmacology Research Unit, a part of the inpatient service of The Johns

Hopkins Hospital. Following the administration of a single dose of 60 mg of WR 6026, serial blood specimens were obtained and urine collections performed in order to assess the pharmacokinetics of this compound. The subjects were monitored for toxicity with clinical laboratory tests of hematology and chemistry variables, along with electrocardiograms, urinalysis, and methemoglobin determinations.

All of the subjects tolerated WR 6026 very well with no adverse symptoms. Two subjects had an increase in the serum AST on the fourth day after drug administration and only one had a corresponding increase in the serum ALT. Two other subjects had minimal elevations of the serum LDH also occurring on the fourth day following drug administration. Whether these elevations were related to laboratory variability or to a delayed effect of the drug is not clear. One subject had an increase in serum triglycerides on the second day following drug administration, but because of a laboratory instrument malfunction, the measurement was not repeated on the fourth day. No subject had a significant change in any of the hematological tests, electrocardiograms, methemoglobin, creatine kinase or urinalysis.

The pharmacokinetic results demonstrated that there was approximately a 30-minute lag time between administration and detectable drug absorption, with peak levels occurring approximately four hours after drug administration. The mean elimination half-time was about 10.5 hours, with a relatively wide range between subjects of 3.6 to 14.5 hours. There was a difference of approximately four-fold in the areas under the plasma concentration-time curves for the eight subjects.

The urinary excretion of the parent drug and two metabolites was quantitated. An average of 11% of dosed drug was recovered as one of these forms, with a range of 5-22%.

In the first two subjects, whole blood as well as plasma concentrations of WR 6026 were measured after dosing. Concentrations in whole blood were lower than those in plasma, indicating that the drug does not become concentrated in the cellular components of blood.

9. <u>Task Order #4</u>

Task Order #4, issued on August 22, 1986, was for the following work:

9.1 To develop a protocol for the study of the pharmacokinetics and pharmacodynamics of sustained, low-dose, intravenous infusions of pyridostigmine.

9.2 Objectives:

9.2.1 To assess the relationship between plasma concentrations of pyridostigmine and cholinesterase inhibition.

9.2.2 To determine whether erythrocyte, skeletal muscle and ocular muscle cholinesterase are inhibited to the same degree by pyridostigmine.

9.2.3 To assess the inter-individual variations in the concentration-effect relations described in 9.2.1 and 9.2.2 above.

We developed a draft protocol entitled "Pharmacokinetics and Pharmacodynamics of Sustained, Low-dose, Intravenous Infusions of Pyridostigmine" and submitted this protocol on August 27, 1986.

The protocol was in the process of being reviewed by the Army at the close of the term of the first "year" of the contract on December 31, 1986.

10. Task Order #5

Task Order #5, issued on September 9, 1986, was for the following work.

10.1 Develop a protocol for the study of the safety, tolerance, pharmacokinetics and pharmacodynamics of a single oral dose of a sustained-release formulation of pyridostigmine. This new sustained-release formulation utilizes a hydrophilic colloid base. There will be four dosage forms to be compared: (1) a "fast" release (6-8 hrs in vitro) tablet of 10 mg; (2) a 'fast" release tablet of 20 mg; (3) a "slow" release (12-14 hrs in vitro) tablet of 10 mg; (4) a "slow" release tablet of 20 mg. A 4-way crossover is suggested.

10.2 Objectives:

10.2.1 To characterize the time-plasma concentration profiles of the four tablets (pharmacokinetic profile).

10.2.2 To characterize the time-RBC cholinesterase inhibition profiles of the four tablets.

A draft protocol entitled "Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Oral Doses of Sustained Release Pyridostigmine in Healthy Men" was developed and was submitted on October 17, 1986.

The protocol was in the process of being reviewed by the Army at the close of the term of the first "year" of the contract on December 31, 1986.

11. Task Order #6

Task Order #6 was issued on September 15, 1986. This task order was produced in close collaboration between the U. S. Army Drug Development Program and our group. It represents our combined efforts at developing a plan that will enhance the efficiency of interacting with the Army to the mutual advantage of both the Army and Johns Hopkins. The task order is entitled "Task Order Management and Administration" and it authorizes the following:

11.1 Design and create clinical protocols.

11.2 Support the USAMRDC drug development program through discussions with the COR for anticipated studies, (which may become future task orders under this contract).

11.3 Develop appropriate background information regarding a particular drug to be tested under the contract, and make suggestions about the protocol to be used.

11.4 Respond to clinical pharmacology inquiries pertaining to current or proposed work. Inquiries would be directed through the COR.

11.5 Writing/drafting protocols.

11.6 Travel to WRAIR, ET to accomplish above.

The work shall commence with notification of the contractor, and will conclude upon the completion of the protocol ready for submission for institutional review (effort beyond this point would be accounted for under a task order to perform that protocol.)

Background development would be in direction(s) identified by the COR.

This task order was implemented at the beginning of the second year of the contract.

DISCUSSION OF THE RESULTS

Results - General

The "first year" of this contract began June 1, 1985 and was extended to December 31, 1986. This contract was established to allow the Division of Clinical Pharmacology at The Johns Hopkins University School of Medicine to assist the USAMRDC in its drug development efforts. In particular, the contract originally was designed to provide the resources and expertise needed to conduct excellent Phase I clinical trials of compounds under development by the Army drug development program. It was our original hope, however, that the interaction between the parties would transcend a simple sponsor-contractor relationship and instead flourish into a collegial relationship wherein a wide variety of current and future compounds and questions would be addressed. We believe that this collegial relationship has, in fact, developed between the Division of Experimental Therapeutics (WRAIR) and the Division of Clinical Pharmacology (J.H.U.) to the mutual benefit of both parties.

Scope of Work

The extent of work anticipated by the Army in the original contract was not realized. We were expecting more protocols and were prepared to implement more protocols than were provided. We believe that we are capable of carrying out a larger number of protocols per year and we have developed, with the Army, a plan that should allow a much more efficient collaboration in the second and third years of the contract. This plan provides for a continual interaction between our unit and the Army with respect to protocol generation and processing.

RESULTS - SPECIFIC

Task Order #1

This task order turned out to be rather ambiguous. A far better task order has since been developed by the Army in consultation with our group. This task order, known as Task Order #6, is being implemented during the second year of the contract and it has replaced Task Order #1.

Task Order #2

This task order was completed efficiently and, in our opinion, the study that constituted this task order is an excellent study. A very effective collaboration was realized

between the U. S. Army Drug Development Program and our group. We believe that our input into the design and implementation of this task order enhanced the information derived from the study with special emphasis on the time course of the effect of pyridostigmine (as well as the pharmacokinetics of pyridostigmine), the relationship between the concentration of drug and the effects on red cell acetylcholinesterase, and the individual variability of both the pharmacokinetics and the pharmacodynamics of the drug.

Task Order #3

This task order, like Task Order #2, was completed efficiently and it also was, in our opinion, an excellent study. Again, positive collaboration was realized in the planning and conduct of this protocol. Although the Division of Experimental Therapeutics, WRAIR was responsible for the major portion of this study design, our input emphasized the value of using extended urine collections to provide data regarding the metabolism of WR 6026 in man. The measurement of metabolites relied on the analytical expertise available at the Division of Experimental Therapeutics, WRAIR.

Task Order #4

This was the first example of a request for our group to generate a protocol that addressed the needs of the U. S. Army Drug Development Program. This protocol was generated with significant collaboration from the Division of Experimental Therapeutics, WRAIR and the study will be implemented in Year 2 of the contract.

Task Order #5

This was the second example of a request for our group to generate a protocol and it also was developed and it also will be implemented in Year 2.

Task Order #6

This task order, as discussed above, has replaced Task Order #1 and has been implemented in Year 2.

CONCLUSIONS

The first term (nineteen months) of this contract has, in our opinion, met the needs of the U. S. Army Drug Development Program as specified in the contract. The Phase I clinical pharmacology studies that were performed, as Task Orders #2 and

#3, were performed efficiently and constitute excellent studies. The protocols that were requested as Task Orders #4 and #5 were provided and those represent additional studies that we anticipate will be carried out in Year 2 of the contract. An excellent working relationship has been developed between our group and the U. S. Army Drug Development Program.

RECOMMENDATIONS

Our recommendation is that the contract be continued. This has been authorized and our second year of the contract has begun. Our recommendations for improving the efficiency of the collaboration between our group and the U. S. Army Drug Development Program have been fully considered and discussed and have, in fact, been incorporated into Task Order #6.

Distribution:

1 copy	Commander U. S. Army Medical Research and Development Command ATTN: SGRD-RMI-S Fort Detrick Frederick, Maryland 21701-5012
1 copy	Commander U. S. Army Medical Materiel Development Activity ATTN:: SGRD-UMS-B Fort Detrick, Frederick, MD 21701-5009
12 copies	Administrator Defense Technical Information Center ATTN: DTIC-DDAC Cameron Station Alexandria, Virginia 22304-6145
1 copy	Director, Walter Reed Army Institute of Research ATTN: SGRD-UWI-F Washington, D.C. 20307-5100

END

7-87

DTIC